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		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR	
☐	L63	L60 and GLAT	2
☐	L62	L60 and copolymer-1	3
☐	L61	L60 and glatiramer	4
☐	L60	(530/324).ccls.	4009
☐	L59	L58 and marker	14
☐	L58	L57 and glatiramer	24
☐	L57	(514/12).ccls.	8659
☐	L56	L54 and copolymer-1	10
☐	L55	L54 and glatiramer	11
☐	L54	(514/2).ccls.	6945
☐	L53	L51 and copolymer-1	3
☐	L52	L51 and glitiramer	0
☐	L51	(424/184.1).ccls.	2536
☐	L50	L48 and copolymer-1	0
☐	L49	L48 and glatiramer	0
☐	L48	(436/15).ccls.	226
☐	L47	L45 and copolymer-1	0
☐	L46	L45 and glatiramer	0
☐	L45	(436/8).ccls.	777
☐	L44	L41 and copolymer-1	4
☐	L43	L41 and copolymer 1	24324904
☐	L42	L41 and glatiramer	8
☐	L41	(435/69.1).ccls.	21722
☐	L40	L36 and GLAT	0
☐	L39	L36 and Cop1	1
☐	L38	L36 and copolymer-1	1
☐	L37	L36 and glatiramer	2
☐	L36	(435/7.92).ccls.	3523
☐	L35	L34 and marker	31
☐	L34	L32 and glatiramer	50
☐	L33	L32 and calibration	5

☐	L32	copaxone	93
☐	L31	(copolymer)adj(1)same(calibration)	25
☐	L30	(lis)adj(dora)	4
☐	L29	(Gad)adj(alexander)	4
☐	L28	6800287.pn.	4
☐	L27	6514938.pn.	3
☐	L26	L23 and copolymer	50
☐	L25	L24 and 13000 daltons	52341
☐	L24	L23 and 4000	50
☐	L23	L22 and permeation	152
☐	L22	L20 and gel	4617
☐	L21	L20 and gel permeation	93486
☐	L20	L19 and alanine	4624
☐	L19	L18 and lysine	4755
☐	L18	L17 and tyrosine	4882
☐	L17	L16 and glutamic	5507
☐	L16	(molecular)adj(weight)adj(markers)	11978
☐	L15	L14 and lysine	26
☐	L14	L13 and tyrosine	27
☐	L13	L12 and glutamic	27
☐	L12	L8 and alanine	29
☐	L11	L10 and alanine	0
☐	L10	L8 and glatiramer	0
☐	L9	L8 and copaxone	0
☐	L8	L6 and copolymer	47
☐	L7	L6 and cop1	0
☐	L6	L5 and markers	418
☐	L5	L4 and calibrating	564
☐	L4	(column)adj(chromatography)	79385
☐	L3	(column)adj(chromatography)same(calibrate)same(markers)	0
	DB=USPT; PLUR=YES; OP=OR		
☐	L2	5800808.pn.	1
☐	L1	5858964.pn.	1

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*ENCOMPPAT2 - EnCompass Patent File 1964-Present (Non-Supporters)

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=> s molecular weight marker
L1 760 MOLECULAR WEIGHT MARKER

=> s l1 and "GLAT"
L2 1 L1 AND "GLAT"

=> d l2 cbib abs

L2 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
2000:227679 Document No. 132:264109 Copolymer 1 related polypeptides for use as **molecular weight markers** and for therapeutic use. Gad, Alexander; Lis, Dora (Yeda Research and Development Co., Ltd., Israel; Teva Pharmaceuticals USA, Inc.). PCT Int. Appl. WO 2000018794 A1 20000406, 72 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US22402 19990924. PRIORITY: US 1998-101693 19980925.

AB The copolymer 1 related polypeptides are capable of binding to HMC class II antigen, HLA-DR1, HLA-DR2, HLA-DR4, or antigen presenting cell. The copolymer 1 related polypeptides are useful as **mol. wt**

. **markers** for accurate determination of the mol. weight of glatiramer acetate and other copolymers. The present invention provides a plurality of **mol. weight markers** for determining the mol. weight of glatiramer acetate and other copolymers which display linear relationships between molar ellipticity and mol. weight, and between retention time and the log of the mol. weight The **mol. wt** . **markers** also optimally demonstrate biol. activity similar to glatiramer acetate or corresponding copolymers and can be used for treating or preventing various immune diseases.

=> s l1 and tyrosine
L3 9 L1 AND TYROSINE

=> s l3 and alaine
L4 0 L3 AND ALAINE

=> s l3 and alanine
L5 0 L3 AND ALANINE

=> s l3 and glutamic acie
L6 0 L3 AND GLUTAMIC ACIE

=> s l3 and lysine
L7 0 L3 AND LYSINE

=> dup remove l3
PROCESSING COMPLETED FOR L3
L8 2 DUP REMOVE L3 (7 DUPLICATES REMOVED)

=> d l8 1-2 cbib abs

L8 ANSWER 1 OF 2 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 1
95135864 EMBASE Document No.: 1995135864. Non-size exclusion effects during gel permeation chromatography of milk protein hydrolysates on an FPLC superose 12 column. O'Callaghan D.M.; Donnelly W.J.; Slattery H.M.; Mulvihill D.M.. Nat. Dairy Products Research Centre, Moorepark,Fermoy, County Cork, Ireland. Journal of Liquid Chromatography Vol. 18, No. 8, pp. 1543-1562 1995.
ISSN: 0148-3919. CODEN: JLCHD8
Pub. Country: United States. Language: English. Summary Language: English.
ED Entered STN: 950531
AB Hydrophobic peptides and aromatic amino acids adsorbed to the matrix of a Superose 12 FPLC column during gel permeation chromatography (GPC) of milk protein hydrolysates. The adsorption phenomenon was most obvious when hydrolysates were prepared using enzyme mixtures which contained exopeptidases. The elution areas of peaks for tryptophan and **tyrosine** from a Superose 12 column was linear with concentration in the range 0 to 1 μmol. ml-1. Amino acid analysis confirmed that a strongly adsorbed peak in the elution profile, measured by absorbance at 280 nm, of an extensively hydrolysed rennet casein contained tryptophan. Individual hydrophobic peptides, used as **molecular weight markers**, also interacted with the column, eluting later than expected. Nitrate in a general water supply used for production of a whey protein hydrolysate on a pilot-scale was responsible for the appearance of an additional peak in the elution profiles from a Superose 12 column, as measured by absorbance at 214 nm.

L8 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 2
93020130. PubMed ID: 1383490. Di-iodo-L-**tyrosine**-labelled dextrans as molecular size markers of nasal absorption in the rat. Fisher A N; Illum L; Davis S S; Schacht E H. (Department of Pharmaceutical Sciences, University of Nottingham, UK.) Journal of pharmacy and pharmacology, (1992 Jul) 44 (7) 550-4. Journal code: 0376363. ISSN:

0022-3573. Pub. country: ENGLAND: United Kingdom. Language: English.
AB A series of fractionated di-iodo-L-**tyrosine**-labelled dextrans (DIT dextrans), with a narrow range of number average molecular weights from 1260 to 45,500 Da, was administered intranasally and intravenously to anaesthetized rats. The nasal absorption of these compounds ranged from 0.6 to 52.7%. There was an inverse relationship between molecular size and the proportion of an intranasal dose absorbed. The study demonstrated the usefulness of DIT dextrans as **molecular weight markers** and confirmed the relationship between molecular size and nasal absorption for highly water soluble compounds. These results also supported the proposition that there is a continuous range of aqueous pores in the nasal mucosa.

```
=> s l1 and coplymer-1
L9            0 L1 AND COPLYMER-1

=> s l1 and calibrate
L10           0 L1 AND CALIBRATE

=> d his

     (FILE 'HOME' ENTERED AT 14:56:51 ON 26 JUL 2005)

     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 14:57:01 ON
     26 JUL 2005
L1          760 S MOLECULAR WEIGHT MARKER
L2            1 S L1 AND "GLAT"
L3            9 S L1 AND TYROSINE
L4            0 S L3 AND ALAINE
L5            0 S L3 AND ALANINE
L6            0 S L3 AND GLUTAMIC ACIE
L7            0 S L3 AND LYSINE
L8            2 DUP REMOVE L3 (7 DUPLICATES REMOVED)
L9            0 S L1 AND COPLYMER-1
L10           0 S L1 AND CALIBRATE

=> s l1 and calibration
L11          36 L1 AND CALIBRATION

=> s l11 and GLAT copolymer
L12           0 L11 AND GLAT COPOLYMER

=> dup remove l11
PROCESSING COMPLETED FOR L11
L13          13 DUP REMOVE L11 (23 DUPLICATES REMOVED)

=> d l13 1-13 cbib abs

L13  ANSWER 1 OF 13  CAPLUS  COPYRIGHT 2005 ACS on STN
1998:450714   Document No. 129:106282  Standard proteins to be used as
     molecular weight markers and isoelectric point
     calibration substances in immunoassays and isoelectric focusing
     techniques.  Uhlenkueken, Jochen; Schmidt, Gerd; Lansing, Manfred
     (Uhlenkueken, Jochen, Germany; Schmidt, Gerd; Lansing, Manfred).  Ger. DE
     19729248 C1 19980709, 6 pp.  (German).  CODEN: GWXXAW.  APPLICATION: DE
     1997-19729248 19970709.
AB   The invention concerns standard proteins or a mixture of standard proteins with
     specific enzyme binding sites, defined mol. weight and isoelec. point for the
     usage as mol. weight markers in electrophoretic
     sepns. combined with immunoblotting and as isoelec. point
     calibration substances in isoelec. focusing.  The proteins
     preserve their enzyme binding properties after denaturizing
     electrophoretic conditions.  One of the properties varies within a mixture;
     enzyme binding, mol. weight or isoelec. point.  The mol. weight of the proteins
```

doubles within a standard series, e.g. 5, 10, 20, 40, 80 and 160 kD. The isoelec. point varies between pH 3-11 in 0.5 pH increments. The standard proteins are recombinant proteins and the invention also concerns the expression vector and the expression of the fusion proteins that are not modified post-transitionally. Thus SDS-PAGE was performed on the analyte and the standard protein mixture; this was followed by blotting onto a methanol saturated PVDF-membrane. After incubation with the primary antibody a secondary antibody labeled with peroxidase was added along with free peroxidase that binds to the standard protein(s). Addition of diaminobenzidin and hydrogen peroxide results the detection of standard proteins and analytes. Alternatevly a step-tag containing gene product was detected after incubation with streptavidin-peroxidase antibody.

L13 ANSWER 2 OF 13 MEDLINE on STN DUPLICATE 1

1998432343. PubMed ID: 9761199. Subnanomolar detection limit for sodium dodecyl sulfate-capillary gel electrophoresis using a fluorogenic, noncovalent dye. Harvey M D; Bandilla D; Banks P R. (Department of Chemistry and Biochemistry, Concordia University, Montreal, QC, Canada.) Electrophoresis, (1998 Sep) 19 (12) 2169-74. Journal code: 8204476. ISSN: 0173-0835. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Picomolar limits of detection are obtained using the noncovalent, fluorogenic dye, Sypro Red. The size separation of four commonly used sodium dodecyl sulfate-capillary gel electrophoresis (SDS-CGE) **molecular weight markers** with 8% linear polyacrylamide (PAA) as the sieving matrix is used to construct a **calibration** curve for molecular weight determinations. SDS-CGE purity and molecular weight determination of purified chorismate mutase-prephenate dehydrogenase (CMPD) from Escherichia coli is shown to be comparable in accuracy with slab gel SDS-polyacrylamide gel electrophoresis (SDS-PAGE). A migration time precision study indicates excellent reproducibility. Sypro red labeling of SDS-bovine serum albumin (SDS-BSA) complexes at nanomolar protein concentrations suggests assay detection limits surpassing those of silver staining. This detectability exceeds that achieved in previous SDS-CGE laser-induced fluorescence studies. This approach is expected to be easily adapted for use with commercial polymer formulations and automated instrumentation.

L13 ANSWER 3 OF 13 MEDLINE on STN DUPLICATE 2

96346753. PubMed ID: 8738333. Quantitation of the water channel protein aquaporin (CHIP28) from red blood cell membranes by densitometry of silver stained polyacrylamide gels. Benga G; Banner M; Wrigglesworth J M. (Department of Cell and Molecular Biology, University of Medicine and Pharmacy, Iuliu Hatieganu, Cluj-Napoca, Romania.) Electrophoresis, (1996 Apr) 17 (4) 715-9. Journal code: 8204476. ISSN: 0173-0835. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB A protein determination procedure which involves the densitometry of silver stained polyacrylamide gels is described. It involves **calibration** with bovine serum albumin and **molecular weight markers** on the same gel with the protein to be quantitated. The procedure is simple, rapid, reproducible and accurate and is more sensitive than other procedures for protein determination. The procedure is particularly useful in quantitating proteins purified in small amounts since the determination can be performed on the same gel used to check the purification. It avoids interference by detergents and other substances usually present in solutions of purified proteins. The procedure has been applied to the quantitation of a recently identified protein, aquaporin (CHIP28), assumed to be a major water channel in the red blood cell membrane. A quantitative analysis of a purified fraction of this protein shows that the 28 kDa component represents approximately two thirds of the protein content of the sample, with the remainder comprising a glycosylated, high molecular mass component. The procedure may be useful for quantitating proteins revealed on silver stained gels and could be included as a standard part of any protocol for protein purification.

L13 ANSWER 4 OF 13 MEDLINE on STN DUPLICATE 3
94325298. PubMed ID: 8049232. Overexpression and purification of the soluble polyhydroxyalkanoate synthase from Alcaligenes eutrophus: evidence for a required posttranslational modification for catalytic activity. Gerngross T U; Snell K D; Peoples O P; Sinskey A J; Csuhai E; Masamune S; Stubbe J. (Department of Biology, Massachusetts Institute of Technology, Cambridge 02139-4307.) Biochemistry, (1994 Aug 9) 33 (31) 9311-20. Journal code: 0370623. ISSN: 0006-2960. Pub. country: United States. Language: English.

AB Polyhydroxyalkanoate (PHA) synthase has been expressed in Escherichia coli by reengineering the 5'-end of the wild-type (wt) gene and subsequent transformation of this gene into protease-deficient E. coli UT5600 (ompT-). Induction with IPTG results in soluble PHA synthase, which is approximately 5% of the total protein. The soluble synthase has been purified to > 90% homogeneity using FPLC chromatography on hydroxylapatite and Q-Sepharose and has a specific activity of 5 mumol min-1 mg-1. The molecular weight of the PHA product is approximately 10(6) Da based on PlGel chromatography and **calibration** using polystyrene **molecular weight markers.** The synthase in the absence of substrate appears to exist in both monomeric and dimeric forms. Incubation of the synthase with an excess of substrate converts it into a form that is now extractable into CHCl3 and sediments on sucrose density ultracentrifugation with PHA. Studies in which the ratio of substrate, 3-D-hydroxybutyrylCoA, to synthase is varied suggest that during polymerization the elongation process occurs at a rate much faster than during the initiation process. A mechanistic model has been proposed for the polymerization process [Griebel, R., Smith, Z., & Merrick, J. (1968) Biochemistry 7, 3676-3681] in which two cysteines are required for catalysis. This model is based on the well-characterized enzymes involved in fatty acid biosynthesis. To test this model, several site-directed mutants of synthase, selected based on sequence conservation among synthases, have been prepared. The C459S mutant has activity approximately 90% that of the wt protein, while the C319S and C319A synthases possess < 0.01% the activity of the wt protein. CD and antibody studies suggest that the mutant proteins are properly folded. The detection of only a single essential cysteine by mutagenesis and the requirement for posttranslational modification by phosphopantetheine to provide a second thiol in many enzymes utilizing coenzyme A thiol ester substrates made us consider the possibility that posttranslational modification was required for synthase activity as well. This hypothesis was confirmed when the plasmid containing PHA synthase (pKAS4) was transformed into E. coli SJ16, requiring beta-alanine for growth. Growth of SJ16/pKAS4 on [3H]-beta-alanine followed by Coomassie staining of the protein and autoradiography revealed that PHA synthase is overexpressed and that beta-alanine is incorporated into the protein. These results suggest PHA synthase is posttranslationally modified by phosphopantetheine. (ABSTRACT TRUNCATED AT 400 WORDS)

L13 ANSWER 5 OF 13 MEDLINE on STN DUPLICATE 4
92059908. PubMed ID: 1952063. Standard **calibration** proteins for Western blotting obtained by genetically prepared protein A conjugates. Lindbladh C; Mosbach K; Bulow L. (Department of Pure and Applied Biochemistry, University of Lund, Sweden.) Analytical biochemistry, (1991 Aug 15) 197 (1) 187-90. Journal code: 0370535. ISSN: 0003-2697. Pub. country: United States. Language: English.

AB Genetically prepared protein A fusion proteins, having retained antibody binding capacity, were used to design different well-defined standard **molecular weight marker** proteins for Western blotting. The blotted marker proteins are developed at the same time and with the same reagents as the protein sample of interest.

L13 ANSWER 6 OF 13 MEDLINE on STN DUPLICATE 5
90145502. PubMed ID: 2619034. Gas-phase sequencing after electroblotting on polyvinylidene difluoride membranes assigns correct molecular weights

to myoglobin **molecular weight markers.**
Kratzin H D; Wiltfang J; Karas M; Neuhoff V; Hilschmann N. (Max-Planck-Institut fur experimentelle Medizin, Abteilung fur Immunchemie, Goettingen, West Germany.) Analytical biochemistry, (1989 Nov 15) 183 (1) 1-8. Journal code: 0370535. ISSN: 0003-2697. Pub. country: United States. Language: English.

AB Commercially available polypeptide marker kits containing peptides generated by cyanogen bromide cleavage of either horse heart myoglobin or sperm whale myoglobin have been investigated by sodium dodecyl sulfate - polyacrylamide gel electrophoresis (SDS-PAGE), followed by electroblotting on polyvinylidene difluoride membranes, and gas-phase sequencing. It could be shown that the molecular weights assigned to the SDS-PAGE bands by the companies are incorrect. Arranged in descending order, the marker kits are composed of the following polypeptide fragments from myoglobin: positions 1-153, 1-131, 56-153, 56-131, 1-55, and 132-153. A polypeptide comprising residues 1-14 was not found. According to these results the log Mr versus Rf plot used for **calibration** must be revised. For the separation of low molecular weight polypeptides and peptides a new gel system based on the theory of multiphasic zone electrophoresis combined with a modified Coomassie staining procedure is reported.

L13 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
1987:614419 Document No. 107:214419 Visualization of molecular weight standards after electroblotting: detection by means of corresponding antibodies. Bjerrum, Ole J.; Hinnerfeldt, Frank R. (Protein Lab., Univ. Copenhagen, Copenhagen, DK-2200, Den.). Electrophoresis, 8(9), 439-44 (English) 1987. CODEN: ELCTDN. ISSN: 0173-0835.

AB The techniques available for detection of mol. weight stds. after blotting are surveyed and evaluated. An identical immunodetection procedure for the antigens as well as for the **mol. weight markers** was evaluated by immunizing rabbits with the whole protein mixture of some com. available **calibration** kits for SDS-PAGE. Antibodies against both high and low-mol.-weight proteins were successfully raised albeit one rabbit failed to generate antibodies against ovalbumin. For immunodetection of rabbit myosin it was necessary to supplement the immunogen with bovine myosin. Best results were obtained by using more than one animal immunized with kits of different origin. Using alkaline phosphatase conjugated secondary antibodies, as little as 0.6 and 1.2 μg of the total low and high-mol.-weight mixture, resp., are necessary for the immunoenzymic detection of all bands. In fused rocket immunoelectrophoresis such antibodies are also useful for determination of the elution position of the **mol. weight markers** in gel filtration expts.

L13 ANSWER 8 OF 13 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
1987:20358 Document No.: PREV198783010292; BA83:10292. RADIOACTIVE REFERENCE PROTEINS FOR THE STUDY OF LABELED PROTEINS BY GEL ELECTROPHORESIS A READY PREPARATION OF RADIOLABELED **CALIBRATION** KITS. PELLON G [Reprint author]; MICHEL G. LABORATOIRE DE BIOCHIMIE MICROBIENNE, UNIV CLAUDE BERNARD-LYON 1, 43 BD DU 11 NOVEMBRE 1918, 69622 VILLEURBANNE CEDEX, FRANCE. Analytical Letters, (1986) Vol. 19, No. 13-14, pp. 1511-1522. CODEN: ANALBP. ISSN: 0003-2719. Language: ENGLISH.

AB The use of unlabelled reference proteins as **molecular weight markers** in the study of radioactive proteins by polyacrylamide gel electrophoresis is rather inconvenient since protein standards should be stained whereas the studied proteins are usually detected by radioautography. We describe a rapid, in vitro method for introducing a radioactive label into reference proteins: amino groups are acylated by a highly radioactive, commercially available reagent: N-succinimidyl-[2,3-3H]propionate. Both standard and studied proteins can then be visualized on a single radioautograph; this allows direct comparison of mobilities, thus improving both convenience and accuracy of Mr determinations, and avoids some major drawbacks of staining, such as the loss of sensitivity of fluorography due to dye-induced quenching. Additionally, in vitro labelling may be used for the detection of proteins

in trace amounts, as an alternative method versus silver staining procedures.

L13 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
1986:125989 Document No. 104:125989 RNA molecular weight determination by agarose gel electrophoresis using formaldehyde as denaturant: comparison of RNA and DNA **molecular weight markers.**
Wicks, Richard J. (Natl. Chem. Res. Lab., CSIR, Pretoria, 0001, S. Afr.). International Journal of Biochemistry, 18(3), 277-8 (English) 1986. CODEN: IJBOBV. ISSN: 0020-711X.
AB When restriction fragments of phage λ DNA and several rRNAs from Escherichia coli and chicken were compared as size markers in the title determination, the DNA restriction fragments were preferable markers because of their sharp bands. However, since DNA migrated slower than RNA of equivalent mol. weight, 0.56 + 106 daltons must be added to the mol. weight obtained from a DNA **calibration** curve to obtain the mol. weight of an RNA sample.

L13 ANSWER 10 OF 13 MEDLINE on STN DUPLICATE 6
85006884. PubMed ID: 6480578. The determination of molecular weight of proteins by gel permeation chromatography in organic solvents. Meredith S C. Journal of biological chemistry, (1984 Oct 10) 259 (19) 11682-5. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB Very amphiphilic proteins with a high tendency to self-aggregate may exist in an aggregated form even in the presence of detergents or denaturants. In order to mitigate the tendency towards self-association, it is necessary to eliminate the amphiphilicity of these proteins. In order to achieve this end, proteins were modified covalently, first by dinitrophenylation followed by permethylation, which rendered the proteins tested soluble in nonpolar organic solvents, such as chloroform/methanol (4/1, v/v). The permethylated 2,4-dinitrophenyl-proteins were then chromatographed using Sepharose CL-6B in chloroform/methanol (4/1, v/v). For ten commonly used **molecular weight marker** proteins, a single symmetrical peak was obtained in the elution profile of the modified proteins, indicating that these products are monodisperse with respect to molecular size. The one exception was gamma globulin which has two polypeptide chains, and thus the elution profile showed two symmetrical peaks. The KD value was found to be a linear function of the logarithm of the molecular weight of the parent protein. From the **calibration** line generated from the **molecular weight marker** proteins, the technique was applied to five highly amphiphilic proteins: bacteriorrhodopsin, uricase, insecticyanin, apolipoprotein B of plasma low density lipoproteins, and band 3 of human erythrocyte membrane, for which the following apparent molecular weights were obtained: 25,000, 31,000, 23,400, 19,000, and 85,000, respectively. These values match the molecular weights obtained from the amino acid sequence in those cases in which the sequence is known. Thus, permethylation in conjunction with organic media disrupts the major driving forces for tertiary and quarternary structure formation in aqueous media, namely, the hydrophobic effect, salt bridges, and hydrogen bonding with the solvent.

L13 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
1981:438305 Document No. 95:38305 High-performance size exclusion chromatography of sea worm chlorocruorin and other large proteins, viruses and polysaccharides on a TSK G5000 PW preparative column. Himmel, Michael E.; Squire, Phil G. (Dep. Biochem., Colorado State Univ., Fort Collins, CO, 80523, USA). Journal of Chromatography, 210(3), 443-52 (English) 1981. CODEN: JOCRAM. ISSN: 0021-9673.
AB The elution parameters of large enzymes, viruses, ribosomes, and other supramol. structures are studied using the preparative TSK G5000 PW type column. The pigmented protein, chlorocruorin, isolated from the sea worm Potamilla leptochaeta, served as an excellent high-**mol.-weight marker** for size-exclusion liquid chromatog. This is

due to its high degree of mol. stability and a mol. weight of 2.9 + 106 determined by sedimentation velocity anal., which is located in a zone formed between viruses and enzymes that is largely devoid of macromol. markers. **Calibration** consts. for this chromatog. column are found for both mol. weight and mol. radii. The data found for hydrodynamic mol. radii are further extended to nonglobular, swollen macromols., such a polysaccharides, using dextran fraction sized by alc. precipitation

L13 ANSWER 12 OF 13 MEDLINE on STN DUPLICATE 7
80006492. PubMed ID: 479121. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis of bovine serum albumin oligomers produced by lipid peroxidation. Janado M; Yano Y; Nakamori H; Nishida T. Journal of biochemistry, (1979 Jul) 86 (1) 177-82. Journal code: 0376600. ISSN: 0021-924X. Pub. country: Japan. Language: English.

AB The oligomers of bovine serum albumin were produced by controlled reaction with peroxidizing linoleic acid to examine their possible utility as **calibration** proteins insodium dodecyl sulfate-polyacrylamide gel electrophoresis. The polymerization was effected in reaction mixtures containing linoleic acid undergoing peroxidation in the presence of ascorbic acid, and conditions that yield soluble oligomers with a wide molecular weight distribution were established. The interaction of these soluble oligomers with sodium dodecyl sulfate exhibited a binding isotherm indistinguishable from that obtained with bovine serum albumin. Furthermore, sodium dodecy sulfate-polyacrylamide gel electrophoresis of the albumin oligomers conformed to the empirical relation of molecular weight to mobility that pertains to the use of these oligomers as standard **molecular weight markers.**

L13 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2005 ACS on STN
1973:13473 Document No. 78:13473 Anomalous behavior of bovine serum albumin in electrophoresis on nondenaturing polyacrylamide gel. Barton, R. J. (Dep. Microbiol., Univ. Reading, Reading, UK). Biochemical Journal, 129(4), 983-5 (English) 1972. CODEN: BIJOAK. ISSN: 0264-6021.

AB Comparison of mol. weight detns. of bovine serum albumin (BSA) polymers with other proteins of known mol. weight, e.g. ovalbumin, by electrophoresis on nondenaturing polyacrylamide gels showed that the BSA polymers do not have electrophoretic mobilities in the system in accord with their mol. wts. They appeared to be of greater size possibly because of steric effects and hence they are unsuitable as **mol. weight markers** . The mol. weight of 265,000 obtained for the 12 S subunit of the coat protein of foot-and-mouth-disease virus using a BSA **calibration** curve (Talbot, P.; Brown, F., 1972) agreed with mol. weight values obtained by other methods since the virus subunits showed similar anomalous behavior to the BSA polymers during electrophoresis.

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=> s "GLAT"
L14          72 "GLAT"

=> s l14 and copaxone
L15          17 L14 AND COPAXONE

=> dup remove l15
PROCESSING COMPLETED FOR L15
L16           7 DUP REMOVE L15 (10 DUPLICATES REMOVED)

=> d l16 1-7 cbib abs
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L16 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
2005:96449 Document No. 142:191246 Preventing graft rejection by combined treatment with synthetic peptide copolymers and immunosuppressants. Aharoni, Rina; Arnon, Ruth; Sela, Michael; Yussim, Alex (Yeda Research and Development Co. Ltd., Israel; Mor Research Applications Ltd.). PCT Int. Appl. WO 2005009333 A2 20050203, 63 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU,

CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-IL695 20040729. PRIORITY: US 2003-2003/PV491236 20030731.

AB The present invention provides compns. and methods for the treatment of graft rejection associated with transplantation of tissues and organs. More specifically, the compns. and methods of the present invention relate to combined treatment involving at least one agent selected from Copolymer 1 (glatiramer acetate), a related heteropolymer or an ordered peptide in combination with at least one addnl. known immunosuppressive agent. The present invention also provides compns. and methods for the treatment of graft rejection using ordered peptides or ordered copolymer 1-related heteropolymers as monotherapy. Glatiramer acetate (GA, copolymer 1, **Copaxone**, **GLAT**) is a well-tolerated drug with a high safety profile currently used for the treatment of multiple sclerosis. This drug suppresses the immune rejection seen in graft vs. host disease and in graft rejection. When used in combination with low doses of cyclosporin A or FK506, this drug is seen to prolong the survival of skin grafts in mice. The time to the appearance of skin rejection was longer than that seen with at least double dose of the immunosuppressive drug alone. The combined treatment also efficiently inhibited the functional deterioration of thyroid grafts in mice, manifested by 2.2- to 20.1-fold increase in iodine absorbance of the transplanted thyroids, as compared to each drug alone. Cardiac allograft survival following the combined treatment with GA and low dose of CyA was longer than the survival obtained by fourfold higher dose of CyA alone. In all transplantation systems, combination therapy of GA with either CyA or FK506 significantly suppressed graft rejection and was more effective than treatment with either GA or the immunosuppressive drug alone, suggesting that such treatment may be beneficial for human transplantation.

L16 ANSWER 2 OF 7 MEDLINE on STN DUPLICATE 1

2004617333. PubMed ID: 15589456. Combined treatment of glatiramer acetate and low doses of immunosuppressive drugs is effective in the prevention of graft rejection. Aharoni Rina; Yussim Alexander; Sela Michael; Arnon Ruth. (The Department of Immunology, The Weizmann Institute of Science, Rehovot, Israel.) International immunopharmacology, (2005 Jan) 5 (1) 23-32. Journal code: 100965259. ISSN: 1567-5769. Pub. country: Netherlands. Language: English.

AB The immunomodulator glatiramer acetate (GA, copolymer 1, **Copaxone**, **GLAT**), currently used for the treatment of multiple sclerosis, is a well-tolerated drug with a high safety profile. We have previously demonstrated that GA suppresses the immune rejection manifested in graft versus host disease, as well as in graft rejection. In an attempt to reduce the dosage and toxicity of the current immunosuppressive regimens, we have now tested the ability of GA, combined with low doses of cyclosporin (CyA) or tacrolimus (FK506), to suppress the rejection of mismatched allografts across major histocompatibility barriers. We report herewith that such combination therapy was effective in several animal models: (1) it led to a significant delay of the vigorous process of skin rejection in mice, manifested by evidential prolongation in skin graft survival (higher than that obtained with at least double dose of the immunosuppressive drug alone). (2) The combined treatment led to efficient inhibition of the functional deterioration of thyroid grafts in mice, manifested by 2.2- to 20.1-fold increase in iodine absorbance of the transplanted thyroids, as compared to each drug alone. (3) Combination therapy inhibited significantly the rejection of vascularized heart transplants in rats. Thus, cardiac allograft survival following the combined treatment with GA and low dose of CyA was longer than the survival obtained by fourfold higher dose of CyA alone. In all transplantation systems, combination therapy of GA with either CyA or

FK506 significantly suppressed graft rejection and was more effective than treatment with either GA or the immunosuppressive drug alone, suggesting that such treatment may be beneficial for human transplantation.

L16 ANSWER 3 OF 7 MEDLINE on STN DUPLICATE 2

2004086522. PubMed ID: 14975587. Induction of IL-10 in rat peritoneal macrophages and dendritic cells by glatiramer acetate. Jung Stefan; Siglienti Ines; Grauer Oliver; Magnus Tim; Scarlato Guglielmo; Toyka Klaus. (Klinische Forschungsgruppe fur Multiple Sklerose an der Neurologischen Klinik, Julius-Maximilians-Universitat Wurzburg, Germany.) Journal of neuroimmunology, (2004 Mar) 148 (1-2) 63-73. Journal code: 8109498. ISSN: 0165-5728. Pub. country: Netherlands. Language: English.

AB Glatiramer acetate (**GLAT**) is a mixture of basic polypeptides that have been shown to suppress experimental autoimmune encephalomyelitis (EAE). As **Copaxone**, **GLAT** is approved for the treatment of relapsing-remitting multiple sclerosis (MS). Different immunomechanisms have been suggested to contribute to the beneficial effects of **GLAT** which rely on blockade of MHC class II molecules or cross-recognition with myelin basic protein (MBP). Because **GLAT** could also inhibit experimental autoimmunity not related to myelin proteins, we searched for additional, less-restricted immunomodulatory actions of **GLAT.** Using freshly isolated resident peritoneal macrophages from naive Lewis rats, it is shown that **GLAT** profoundly modulates cytokine secretion of the cells. In unseparated macrophages (MPhi) and MPhi of low density, **GLAT** enhanced constitutive and LPS-induced production of interleukin 10 (IL-10) while LPS-induced synthesis of tumor necrosis factor-alpha (TNF-alpha) was dose-dependently suppressed by **GLAT.** Although both basic proteins **GLAT** and MBP facilitated adherence of MPhi, MBP had opposite effects on cytokine production suggesting unique properties of **GLAT.** In contrast to MPhi, peritoneal mast cells produced only little amounts of cytokines. The inductive effect of **GLAT** on IL-10 production by antigen-presenting cells was also observed in bone marrow-derived rat dendritic cells (DCs) which, unlike MPhi, were not suppressed in their production of TNF-alpha. Induction of IL-10 in different antigen-presenting cells is a new immunomodulatory mechanism of **GLAT.** In part, it goes along with the inhibition of TNF-alpha and may be a common basis for the known beneficial effects of **GLAT** on various cellular autoimmune responses including MS.

L16 ANSWER 4 OF 7 EMBASE on STN

2003514873 EMBASE [Glatirameracetate and Mitoxantron in MS-therapy]. GLATIRAMERACETAT UND MITOXANTRON IN DER BEHANDLUNG DER MULTIPLEN SKLEROSE. Neundorfer B.. Dr. B. Neundorfer, Neurologische Klinik mit Poliklinik, Universitat Erlangen-Nurnberg, Schwabachanlage 6, 91054 Erlangen, Germany. Nervenheilkunde Vol. 22, No. 10, pp. 504-508 2003.
Refs: 51.
ISSN: 0722-1541. CODEN: NERVDI
Pub. Country: Germany. Language: German. Summary Language: English; German.

ED Entered STN: 20040105

AB Glatirameracetate (with the trademark Capaxone® in Germany) is a myelinbasic analogon which suppresses the developping of experimental autoimmune encephalomyelitis (EAE) in animal experiments. It binds to the major histocompatibility complex (MHC) molecules of antigen-presenting cells and induces a shift from TH1- to TH2-cells. **GLAT** has shown therapeutic efficacy in MS-patients in double blinded randomised controlled clinical studies with reduction of the annual rate of exacerbating and of GD-enhancing lesions in MRT. Mitoxantron (Mx) is a synthetic antrachinone, which inhibits the DNA replication and blocks the synthesis of messenger RNA. It suppresses the development of B-lymphozytes and of CD4 positive helper cells. In animal experiments it inhibits the development of EAE. In MS-patients Mx improves both clinical and MRI indices of disease activity, in particular in combination with

methylprednisolone.

L16 ANSWER 5 OF 7 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
2003:574214 The Genuine Article (R) Number: 614JK. **GLAT** (**Copaxone**) for treatment of steroid-refractory acute graft versus host disease.. Johnston L J (Reprint); Shizuru J S; Stockerl-Goldstein K E; Stuart M J; Gasparetto C; Long G D; Rizzieri D A; Vredenburgh J J; Blume K G; Negrin R S; Chao N J. Stanford Univ, Stanford, CA 94305 USA; Duke Univ, Durham, NC 27706 USA. BLOOD (16 NOV 2002) Vol. 100, No. 11, Part 1, pp. 421A-421A. MA 1631. ISSN: 0006-4971. Publisher: AMER SOC HEMATOLOGY, 1900 M STREET. NW SUITE 200, WASHINGTON, DC 20036 USA. Language: English.

L16 ANSWER 6 OF 7 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 3
2002338506 EMBASE [Immunotherapy of multiple sclerosis with glatiramer acetate mechanisms of action and results from therapeutic trials]. IMMUNTHERAPIE DER MULTIPLEN SKLEROSE MIT GLATIRAMERAZETAT (**COPAXONE**.RTM.): WIRKMECHANISMEN UND ERGEBNISSE AUS THERAPIESTUDIEN. Gold R.; Heidenreich F.; Kappos L.. Dr. R. Gold, Neurologische Universitatsklinik, Josef-Schneider-Strasse 11, 97080 Wurzburg, Germany. r.gold@mail.uni-wuerzburg.de. Aktuelle Neurologie Vol. 29, No. 7, pp. 345-351 2002.
Refs: 31.
ISSN: 0302-4350. CODEN: AKNUAR
Pub. Country: Germany. Language: German. Summary Language: English; German.
ED Entered STN: 20021010
AB Amongst immunomodulatory drugs used in multiple sclerosis (MS), glatiramer acetate (**GLAT**: former name: Copolymer-1: trademark **Copaxone**) has the longest history. Even today its mechanisms of action are only incompletely understood. **GLAT** has shown therapeutic efficacy in diverse models of experimental autoimmune encephalomyelitis (EAE). At the cellular level **GLAT** induces a shift from TH1 to TH2 cytokines. Therapeutic efficacy in relapsing-remitting MS patients has been proven by controlled clinical studies. Here we review current aspects of **GLAT** therapy and discuss its role in immunomodulatory treatment of MS.

L16 ANSWER 7 OF 7 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2003:336231 Document No.: PREV200300336231. **GLAT** (**Copaxone**) for Treatment of Steroid-Refractory Acute Graft Versus Host Disease. Johnston, Laura J. [Reprint Author]; Shizuru, Judith S. [Reprint Author]; Stockerl-Goldstein, Keith E. [Reprint Author]; Stuart, Monic J. [Reprint Author]; Gasparetto, Cristina [Reprint Author]; Long, Gwynn D. [Reprint Author]; Rizzieri, David A. [Reprint Author]; Vredenburgh, James J. [Reprint Author]; Blume, Karl G. [Reprint Author]; Negrin, Robert S. [Reprint Author]; Chao, Nelson J. [Reprint Author]. Bone Marrow Transplantation, Stanford University, Stanford, CA, USA. Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 1631. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.
AB Acute graft-versus-host disease (AGVHD) remains a significant cause of morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT). AGVHD (gtoreq grade II) occurs in 10-50% of allogeneic HCT recipients despite prophylactic immunosuppression. Glucocorticoids are the most effective therapy for AGVHD. Patients who do not respond to glucocorticoids may be faced with 80% non-relapse mortality. We have conducted a clinical Phase I trial using the synthetic polymer, **GLAT**, for the treatment of steroid-refractory AGVHD. Twelve patients received **GLAT** as therapy for AGVHD at Stanford or Duke University. Five patients had failed one prior AGVHD therapy and

seven had failed two to five prior AGVHD therapies. All patients failed four or more days of corticosteroid treatment at 2 mg/kg/d (9 patients) or 1 mg/kg/d (3 patients) with a calcineurin inhibitor. Five patients had grade III skin-only AGVHD. All five patients responded, three with complete resolution of AGHVD although one received concomitant photopheresis, one with a sustained partial remission (PR) and one with a transient three week PR. Seven patients had overall grade IV AGVHD involving the skin, gut or liver. Five of these seven patients had responses, three with complete resolution and two with transient resolution of 30 and 50 days. Two patients had no response. Eleven patients have died. Four patients died of progressive GVHD with or without infectious complications (2 cytomegalovirus, 1 aspergillus). One CR patient died with probable pulmonary chronic GVHD. The remaining patients died of relapsed malignancy (3), bacterial infection (2) or interstitial pneumonia (1). One patient was alive ten months following transplantation without active GVHD. Dose escalation of **GLAT** from 20 to 80 mg/day was achieved without dose limiting toxicities. In summary, **GLAT** has efficacy in patients with steroid-refractory AGVHD of the skin, gut and liver with a sustained response in seven of twelve patients without identifiable toxicity. Unfortunately, the prognosis of patients with steroid refractory acute GVHD is guarded. In this small phase I trial **GLAT** did not improve the expected poor outcome for patients with refractory AGVHD, however, the preliminary data may support the use of **GLAT** earlier in the course of AGVHD.

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=> s glatiramer acetate
L17       1464 GLATIRAMER ACETATE

=> s l17 and calibration
L18          0 L17 AND CALIBRATION

=> s l17 and markers
L19         56 L17 AND MARKERS

=> dup remove l19
PROCESSING COMPLETED FOR L19
L20          23 DUP REMOVE L19 (33 DUPLICATES REMOVED)

=> d l20 1-23 cbib abs

L20  ANSWER 1 OF 23  BIOSIS  COPYRIGHT (c) 2005 The Thomson Corporation  on STN
2004:431241  Document No.: PREV200400435798. Copolymer 1 related polypeptides
     for use as molecular weight markers and for therapeutic use.
     Gad, Alexander [Inventor, Reprint Author]; Lis, Dora [Inventor]. Nes
     Ziona, Israel. ASSIGNEE: Yeda Research and Development Co., Ltd., Rehovot,
     Israel. Patent Info.: US 6800287 20041005. Official Gazette of the United
     States Patent and Trademark Office Patents, (Oct 5 2004) Vol. 1287, No. 1.
     http://www.uspto.gov/web/menu/patdata.html. e-file.
     ISSN: 0098-1133 (ISSN print). Language: English.
AB   The present invention provides molecular weight markers for
     accurate determination of the molecular weight of glatiramer
     acetate and other copolymers. The present invention further
     provides a plurality of molecular weight markers for determining
     the molecular weight of glatiramer acetate and other
     copolymers which display linear relationships between molar ellipticity
     and molecular weight, and between retention time and the log of the
     molecular weight. The molecular weight markers also optimally
     demonstrate biological activity similar to glatiramer
     acetate or corresponding copolymers and can be used for treating
     or preventing various immune diseases.

L20  ANSWER 2 OF 23  CAPLUS  COPYRIGHT 2005 ACS on STN
2004:287758  Document No. 140:302345  Genes showing altered patterns of
     expression in the central nervous system in multiple sclerosis and their
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diagnostic and therapeutic use. Dangond, Fernando; Hwang, Daehee; Gullans, Steven R. (Brigham and Women's Hospital, Inc., USA). PCT Int. Appl. WO 2004028339 A2 20040408, 139 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US29451 20030925. PRIORITY: US 2002-2002/PV414219 20020927.

AB The present invention identifies a number of gene **markers** whose expression is altered in multiple sclerosis (MS). These **markers** can be used to diagnose or predict MS in subjects, and can be used in the monitoring of therapies. In addition, these genes identify therapeutic targets, the modification of which may prevent MS development or progression.

L20 ANSWER 3 OF 23 MEDLINE on STN DUPLICATE 1

2004501938. PubMed ID: 15306684. Autoimmune concepts of multiple sclerosis as a basis for selective immunotherapy: from pipe dreams to (therapeutic) pipelines. Hohlfeld Reinhard; Wekerle Hartmut. (Department of Neuroimmunology, Max Planck Institute for Neurobiology, Am Klopferspitz, D-82152 Martinsried, Germany.. reinhard.hohlfeld@med.uni-muenchen.de) . Proceedings of the National Academy of Sciences of the United States of America, (2004 Oct 5) 101 Suppl 2 14599-606. Electronic Publication: 2004-08-11. Ref: 164. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Autoimmune T and B cell responses to CNS antigen(s) are thought to drive the pathogenesis of multiple sclerosis (MS), and thus are logical targets for therapy. Indeed, several immunomodulatory agents, including IFN-beta 1b, IFN-beta 1a, **glatiramer acetate**, and mitoxantrone, have had beneficial clinical effects in different forms of MS. However, because the available treatments are only partially effective, MS therapy needs to be further improved. Selective (antigen-specific) immunotherapies are especially appealing because in theory they combine maximal efficacy with minimal side effects. Indeed, several innovative immunotherapies have been successfully applied in experimental autoimmune encephalomyelitis. For example, autoreactive T cells can be selectively targeted by means of antigen, T cell receptor, or activation **markers.** However, experimental autoimmune encephalomyelitis is far from being a perfect approximation of MS because MS is more heterogeneous and the target antigen(s) is (are) not known. Further advances in MS therapy will depend on our growing understanding of the pathogenesis of this still incurable disease.

L20 ANSWER 4 OF 23 MEDLINE on STN DUPLICATE 2

2004267606. PubMed ID: 15090474. Multiple sclerosis: **glatiramer acetate** inhibits monocyte reactivity in vitro and in vivo. Weber Martin S; Starck Michaela; Wagenpfeil Stefan; Meinl Edgar; Hohlfeld Reinhard; Farina Cinthia. (Institute for Clinical Neuroimmunology, Marchioninistrasse 15, D-81377 Munich, Germany.. hohlfeld@neuro.mpg.de) . Brain; a journal of neurology, (2004 Jun) 127 (Pt 6) 1370-8. Electronic Publication: 2004-04-16. Journal code: 0372537. ISSN: 0006-8950. Pub. country: England: United Kingdom. Language: English.

AB It is widely assumed that **glatiramer acetate** (GA), an approved agent for the immunomodulatory treatment of multiple sclerosis, acts primarily as an antigen for T lymphocytes. Recent studies, however, indicated that in vitro, GA directly inhibits dendritic cells, a rare but potent type of professional antigen-presenting cell (APC). To investigate whether these in vitro observations are relevant to the actions of GA in vivo, we studied the effects of GA on monocytes, the major type of circulating APC. In a first series of experiments, we investigated the effects of GA on monocyte reactivity in vitro. Monocytes were stimulated

with ligands for Toll-like receptor (TLR)-2 (peptidoglycan and lipoteichoic acid), TLR-4 [lipopolysaccharide (LPS)] and TLR-5 (flagellin), as well as two proinflammatory cytokines (interferon-gamma and granulocyte-monocyte colony-stimulating factor). Monocyte activation was measured by induction of the surface **markers** signalling lymphocytic activation molecule (SLAM), CD25 and CD69 (detected by cytofluorometry), and by production of monocyte-derived tumour necrosis factor (TNF)-alpha (detected by enzyme-linked immunospot assay). GA had a broad inhibitory effect on all measures of monocyte reactivity, regardless of which stimulator was used. It is unlikely that this reflects a simple toxic effect, because monocyte viability and CD14 expression were unaffected. In a second series of experiments, we investigated the properties of monocytes cultured ex vivo from eight GA-treated multiple sclerosis patients, eight untreated multiple sclerosis patients and eight healthy subjects. We found that LPS-induced SLAM expression and TNF-alpha production were significantly reduced in monocytes from GA-treated patients compared with controls. These results demonstrate for the first time that GA inhibits monocyte reactivity in vitro and in vivo, significantly extending the current concept of the mechanism of action of GA.

L20 ANSWER 5 OF 23 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

2004:571461 The Genuine Article (R) Number: 831MK. Bio-**markers** of disease activity and response to therapy in multiple sclerosis. Miller A (Reprint); Glass-Marmor L; Abraham M; Grossman I; Shapiro S; Galboiz Y. Technion Israel Inst Technol, Fac Med, Div Neuroimmunol, 7 Michal St, IL-34362 Haifa, Israel (Reprint); Technion Israel Inst Technol, Fac Med, Div Neuroimmunol, IL-34362 Haifa, Israel; Technion Israel Inst Technol, Fac Med, Rappaport Inst Res Med Sci, Carmel Med Ctr, Multiple Sclerosis Ctr, IL-34362 Haifa, Israel. millera@tx.technion.ac.il. CLINICAL NEUROLOGY AND NEUROSURGERY (JUN 2004) Vol. 106, No. 3, Sp. iss. SI, pp. 249-254. ISSN: 0303-8467. Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. Language: English.

L20 ANSWER 6 OF 23 MEDLINE on STN

2004322118. PubMed ID: 15223245. Gene expression profiling of relevant biomarkers for treatment evaluation in multiple sclerosis. Hong Jian; Zang Ying C Q; Hutton George; Rivera Victor M; Zhang Jingwu Z. (Department of Neurology and Baylor-Methodist Multiple Sclerosis Center, Baylor College of Medicine, Houston, TX 77030, USA.) Journal of neuroimmunology, (2004 Jul) 152 (1-2) 126-39. Journal code: 8109498. ISSN: 0165-5728. Pub. country: Netherlands. Language: English.

AB Multiple sclerosis (MS) is thought to correlate with an array of clinically relevant biomarkers produced during inflammatory process. In this study, a novel gene expression profiling technology was developed and characterized to quantitatively measure the expression profiles of 34 genes selected based on their role in inflammation and their susceptibility to regulation by current MS treatment agents, beta-interferon (IFN) and **glatiramer acetate** (GA).
Potential clinical applications of the technology were evaluated by in vitro and ex vivo analyses in peripheral blood mononuclear cells (PBMC) obtained from MS patients and controls. Interferon-inducible genes were universally up-regulated after in vitro treatment with beta-IFN while the expression of other selected genes encoding cytokines and molecules related to T cell trafficking, activation and apoptosis was variably affected. Beta-IFN and GA exhibited distinctive and characteristic regulatory effects on the expression of the selected genes. Similar regulatory properties of beta-IFN and GA were seen by ex vivo analysis of PBMC specimens in a self-paired study by comparing specific changes induced by beta-IFN or GA treatment in the same patients as well as in a group study by measuring specific profiles in treatment groups compared with an untreated group. Furthermore, the technology served as a simple and sensitive assay for detection of beta-IFN neutralizing antibody based on the blocking effect of serum antibodies on the known regulatory

properties of beta-IFN on PBMC. The findings provide important information on the immunoregulatory properties of beta-IFN and GA and support potential clinical applications of this technology in detection of neutralizing antibody (NAB) and evaluation of treatment responses in MS patients.

L20 ANSWER 7 OF 23 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

2004:624652 The Genuine Article (R) Number: 834KW. Regulation of gene expression associated with acute experimental autoimmune encephalomyelitis by Lovastatin. Paintlia A S; Paintlia M K; Singh A K; Stanislaus R; Gilg A G; Barbosa E; Singh I (Reprint). Med Univ S Carolina, Dept Pediat, 96 Jonathan Lucas St, CSB-316, Charleston, SC 29425 USA (Reprint); Med Univ S Carolina, Dept Pediat, Charleston, SC 29425 USA; Med Univ S Carolina, Dept Pathol & Lab Med, Charleston, SC 29425 USA; Ralph H Johnson VA Med Ctr, Charleston, SC USA. singhi@musc.edu. JOURNAL OF NEUROSCIENCE RESEARCH (1 JUL 2004) Vol. 77, No. 1, pp. 63-81. ISSN: 0360-4012. Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 111 RIVER ST, HOBOKEN, NJ 07030 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The attenuation of experimental autoimmune encephalomyelitis (EAE) by Lovastatin (LOV) has now been well established. The present study was designed to explore the global effect of LOV treatment on expression of immune-related genes in lumbar spinal cord (LSC) during acute EAE by using Affymetrix DNA microarrays. LOV treatment demonstrated the limited infiltration of inflammatory cells into the LSC, and microarray analysis further validated those interpretations by demonstrating relatively less alteration in expression of immune response genes in LOV-treated EAE rats on peak clinical day and recovery vs. untreated EAE counterparts. There was significant change in expression of about 158 immune-related genes (including 127 genes reported earlier) in LOV-treated vs. untreated EAE (>1.5 or <-1.5 fold change; P less than or equal to .05), of which 140 genes were suppressed and only 18 genes were up-regulated. These altered genes encode for leukocyte-specific **markers** and receptors, histocompatibility complex, cytokines/receptors, chemokines/receptors, adhesion molecules, components of the complement cascade, cellular activation, and transcription factors and signal transduction-related molecules. Interestingly, T(H)2 phenotype cytokines such as interleukin-4, interleukin-10, and transforming growth factor-beta1 and transcription factors such as peroxisome proliferator-activated receptor (PPAR)-gamma were upregulated in LSC by LOV treatment as further revealed by real-time PCR and immunoblotting. These findings indicate that PPARs may be mediating the anti inflammatory and immunomodulatory effects of LOV. Together, these findings provide new insight into the molecular events associated with the protection provided by statins during treatment of demyelinating diseases such as multiple sclerosis. (C) 2004 Wiley-Liss, Inc.

L20 ANSWER 8 OF 23 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

2004:883691 The Genuine Article (R) Number: 859VY. Assessing treatment effects on axonal loss - evidence from MRI monitored clinical trials. Barkhof F (Reprint). Free Univ Amsterdam Hosp, Dept Diagnost Radiol, POB 7057, Boelelaan 1117, NL-1007 MB Amsterdam, Netherlands (Reprint); Free Univ Amsterdam Hosp, Dept Diagnost Radiol, NL-1007 MB Amsterdam, Netherlands. f.barkhof@vumc.nl. JOURNAL OF NEUROLOGY (SEP 2004) Vol. 251, Supp. [4], pp. 6-12. ISSN: 0340-5354. Publisher: DR DIETRICH STEINKOPFF VERLAG, PO BOX 10 04 62, D-64204 DARMSTADT, GERMANY. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Magnetic resonance imaging (MRI) is a collection of very sensitive and versatile techniques for detecting multiple sclerosis (MS) related damage in the central nervous system. Each technique is characterised by a particular combination of sensitivity, tissue and pathological specificity, and technical requirements that enable diverse aspects of MS to be explored.

MRI techniques also offer the possibility of quantitatively assessing the effects of therapeutic interventions, and to correlate these effects to clinical outcomes. Of special interest are newer MR techniques that correlate more strongly with disability than gadolinium-enhancement and T2 lesion load, and this review focuses on T1 hypointense lesions, MR spectroscopy, and brain atrophy as surrogate **markers** of axonal loss, and their application in randomised clinical trials.

Several disease-modifying therapies appear to have differential effects on inflammation, demyelination and axonal loss as judged by MRI, illustrating the unique capability of MRI to interrogate the pathophysiology of MS. At the same time it illustrates the difficulties in understanding the mechanisms leading to axonal loss and persistent clinical deficit.

L20 ANSWER 9 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

2003:129777 Document No.: PREV200300129777. Copolymer 1 related polypeptides for use as molecular weight **markers** and for therapeutic use. Gad, Alexander [Inventor, Reprint Author]; Lis, Dora [Inventor]. Nes Ziona, Israel. ASSIGNEE: Yeda Research and Development Co. Ltd. at the Weizmann Institute of Science, Israel. Patent Info.: US 6514938 20030204. Official Gazette of the United States Patent and Trademark Office Patents, (Feb 4 2003) Vol. 1267, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file.

ISSN: 0098-1133 (ISSN print). Language: English.

AB The present invention provides molecular weight **markers** for accurate determination of the molecular weight of **glatiramer acetate** and other copolymers. The present invention further provides a plurality of molecular weight **markers** for determining the molecular weight of **glatiramer acetate** and other copolymers which display linear relationships between molar ellipticity and molecular weight, and between retention time and the log of the molecular weight. The molecular weight **markers** also optimally demonstrate biological activity similar to **glatiramer acetate** or corresponding copolymers and can be used for treating or preventing various immune diseases. In addition, the subject invention provides pharmaceutical compositions for the treatment of immune diseases comprising a polypeptide having an identified molecular weight and an amino acid composition corresponding to **glatiramer acetate** or a terpolymer.

L20 ANSWER 10 OF 23 MEDLINE on STN DUPLICATE 3

2004007964. PubMed ID: 14704481. Effect of immunomodulatory treatment of multiple sclerosis on lymphocyte surface immunomarkers. Michalowska-Wender Grazyna; Losy Jacek; Wender Mieczyslaw; Januszkiewicz-Lewandowska Danuta; Nowak Jerzy. (Department of Clinical Neuroimmunology, University of Medical Science, Przybyszewskiego 49, PL 60-355 Poznan, Poland.. mwender@amp.edu.pl) . Polish journal of pharmacology, (2003 Sep-Oct) 55 (5) 877-80. Journal code: 9313882. ISSN: 1230-6002. Pub. country: Poland. Language: English.

AB The aim of this study was to analyze the effect of immunomodulatory treatment of multiple sclerosis (MS) on lymphocyte surface immunomarkers. The special attention was given to TCR alpha/beta, gamma/delta and alpha/beta HLA-DR **markers.** Peripheral blood was obtained from 39 patients with clinically definite R-R MS, fulfilling the criteria of McDonald et al.[5]. The group of 15 patients was treated with interferon beta-1a (Avonex) intramuscularly once a week. The blood was obtained before and after two years of treatment. The other group of 10 patients was treated every day with 20 mg of **glatiramer acetate** (Copaxone) intracutaneously. Subsets of lymphocytes were analyzed by the method of flow cytometry, using monoclonal antibodies produced by Ortho Diagnostic System. The relative results were evaluated using Immuno Count II program. The frequency of the studied subsets in MS was markedly different from that in healthy persons. The higher number of CD4, TCR alpha/beta positive cells and higher CD4/CD8 ratio was observed. In comparison to healthy individuals, in MS patients a decreased number of

TCR gamma/delta, and alpha/beta HLA-DR was found. After therapy with **glatiramer acetate**, CD3 and CD8 positive lymphocytes were more frequently observed than before the drug administration. The CD4/CD8 ratio was markedly decreased. The effect of interferon beta-1a treatment was similar as in the previous group, i.e. a slight increase in CD3 and CD8 was noticed after therapy. Despite the differences in action of both immunomodulatory drugs, which was established in several studies, we like to stress some similarity in their effect on CD3, CD8, alpha/beta HLA-DR and gamma/delta HLA-DR immunomarkers frequency in lymphocyte, and on the CD4/CD8 ratio. This may mean that there are some common immunological steps of special importance for the clinical effect in MS.

L20 ANSWER 11 OF 23 MEDLINE on STN DUPLICATE 4

2003333269. PubMed ID: 12864985. **Glatiramer acetate** -reactive peripheral blood mononuclear cells respond to multiple myelin antigens with a Th2-biased phenotype. Dhib-Jalbut Suhayl; Chen Man; Said Areen; Zhan Min; Johnson Kenneth P; Martin Roland. (University of Maryland School of Medicine, Baltimore, MD 21201, USA.. sjalbut@umaryland.edu) . Journal of neuroimmunology, (2003 Jul) 140 (1-2) 163-71. Journal code: 8109498. ISSN: 0165-5728. Pub. country: Netherlands. Language: English.

AB One favored mechanism of action of **glatiramer acetate** (GA) in multiple sclerosis (MS) involves the induction of GA-reactive Th2 cells that are believed to enter the central nervous system and mediate bystander suppression in response to cross-reactive myelin antigens. To test this hypothesis, we examined the proliferative response and cytokine release from peripheral blood mononuclear cells (PBMCs) of 12 MS patients treated with GA, in response to 16 myelin peptides that were previously described as immunodominant or encephalitogenic and a tetanus peptide as a control antigen. Interferon-gamma (IFN-gamma) and IL-5 (**markers** of Th1 and Th2 responses, respectively) were assayed by enzyme-linked immunosorbent assay (ELISA). GA-stimulated PBMCs from 9 of 12 patients (75%) proliferated to one or more myelin peptides. Among the 16 peptides tested, GA-stimulated PBMCs from the majority of the patients proliferated in response to MOG(21-44). PBMCs from two thirds of the patients produced IL-5 in response to myelin peptides, while half of them produced IFN-gamma. Th1/Th0/Th2 cytokine phenotypes demonstrated that responses from 10 of 12 patients were either Th0- or Th2-biased. Responses from two patients were Th1-biased. Conversely, some myelin-specific T-cell lines (TCLs) responded to GA by proliferation (3 of 21 TCLs), IL-5 release (11 of 21 TCLs), and IFN-gamma release (3 of 21 TCLs). These results indicate that GA-reactive TCLs can respond to a spectrum of myelin peptides in a Th2-biased fashion, which is consistent with the concept of bystander suppression. Furthermore, some myelin-specific TCLs are able to recognize GA, with a tendency to produce more IL-5 than IFN-gamma, which would suggest a systemic modulatory effect of the drug.

L20 ANSWER 12 OF 23 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

2003:342468 The Genuine Article (R) Number: 666QC. Predicting multiple sclerosis at optic neuritis onset. Jin Y P (Reprint); de Pedro-Cuesta J; Huang Y H; Soderstrom M. Huddinge Univ Hosp, Div Neurol, Karolinska Inst, R54, S-14186 Huddinge, Sweden (Reprint); Huddinge Univ Hosp, Div Neurol, Karolinska Inst, S-14186 Huddinge, Sweden; Huddinge Univ Hosp, Div Ophthalmol, S-14186 Huddinge, Sweden; Carlos III Inst Hlth, Natl Ctr Epidemiol, Dept Appl Epidemiol, Madrid, Spain; Chongqing Univ Med Sci, Div Med Stat, Chongqing, Peoples R China. MULTIPLE SCLEROSIS (MAR 2003) Vol. 9, No. 2, pp. 135-141. ISSN: 1352-4585. Publisher: ARNOLD, HODDER HEADLINE PLC, 338 EUSTON ROAD, LONDON NW1 3BH, ENGLAND. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Using multivariate analyses, individual risk of clinically definite multiple sclerosis (CDMS) after monosymptomatic optic neuritis (MON) was quantified in a prospective study with clinical MON onset during 1990-95 in Stockholm, Sweden. During a mean follow-up time of 3.8 years, the presence of MS-like brain magnetic resonance imaging (MRI) lesions and oligoclonal immunoglobulin (Ig) G bands in cerebrospinal fluid (CSF) were

strong prognostic **markers** of CDMS, with relative hazard ratios of 4.68 [95% confidence interval (0) 2.21-9.91] and 5.39 (95% Cl 1.56-18.61), respectively. Age and season of clinical onset were also significant predictors, with relative hazard ratios of 1.76 (95% Cl 1.02-3.04) and 2.21 (95% Cl 1.13-3.98), respectively. Based on the above two strong predictors, individual probability of CDMS development after MON was calculated in a three-quarter sample drawn from a cohort, with completion of follow-up at three years. The highest probability, 0.66 (95% Cl 0.48-0.80), was obtained for individuals presenting with three or more brain MRI lesions and oligoclonal bands in the CSF and the lowest, 0.09 (95% Cl 0.02-0.32), for those not presenting with these traits. Medium values, 0.29 (95% Cl 0.13-0.53) and 0.32 (95% Cl 0.07-0.73), were obtained for individuals discordant for the presence of brain MRI lesions and oligoclonal bands in the CSF These predictions were validated in an external one-quarter sample.

L20 ANSWER 13 OF 23 MEDLINE on STN DUPLICATE 5

2003047978. PubMed ID: 12533330. Short-term correlations between clinical and MR imaging findings in relapsing-remitting multiple sclerosis. Rovaris Marco; Comi Giancarlo; Ladkani David; Wolinsky Jerry S; Filippi Massimo. (Neuroimaging Research Unit, Department of Neuroscience, Scientific Institute and University Ospedale San Raffaele, Milan, Italy. (European/Canadian Glatiramer Acetate Study Group).) AJNR. American journal of neuroradiology, (2003 Jan) 24 (1) 75-81. Journal code: 8003708. ISSN: 0195-6108. Pub. country: United States. Language: English.

AB BACKGROUND AND PURPOSE: Despite extensive use of MR imaging to provide **markers** of multiple sclerosis (MS) activity and accumulated disease burden, the magnitude of the relationship between clinical and MR findings is still debated. Using data from the European/Canadian **glatiramer acetate** (GA) trial, we investigated short-term correlations between clinical and MR measures of disease activity in patients with relapsing-remitting MS (RRMS). METHODS: In a 9-month, double-blinded, placebo-controlled study, 239 patients with RRMS were randomly assigned to receive 20 mg GA (n = 119) or placebo (n = 120). Clinical assessment included monthly neurologic examinations with Expanded Disability Status Scale scoring and visits for symptoms suggestive of relapse. Dual-echo T2-weighted and pre- and postcontrast T1-weighted brain MR images were obtained at baseline and monthly during follow-up. Contrast-enhancing and new T2-hyperintense lesions were counted, and total T2-hyperintense and T1-hypointense lesion volumes were measured. RESULTS: Significant univariate correlations were found between the number of relapses during the study period and the number of enhancing lesions at baseline (r = 0.25) and during follow-up (r = 0.30) in the study population as a whole. Multivariable analysis showed that two independent factors were more strongly correlated with relapse frequency: the number of relapses during the 2 years before entry and the number of on-trial enhancing lesions, in the whole study population and in the placebo group. CONCLUSION: In RRMS, MR imaging measures of inflammatory activity are modestly but significantly correlated with the occurrence of clinical attacks over the short term. Clinical and MR imaging assessment can provide complementary outcome measures for RRMS trials.

L20 ANSWER 14 OF 23 MEDLINE on STN

2002660070. PubMed ID: 12420101. Immunological assay for assessing the efficacy of **glatiramer acetate** (Copaxone) in multiple sclerosis. A pilot study. Farina Cinthia; Wagenpfeil Stefan; Hohlfeld Reinhard. (Department of Neuroimmunology, Max-Planck-Institute of Neurobiology, Martinsried, Germany.) Journal of neurology, (2002 Nov) 249 (11) 1587-92. Journal code: 0423161. ISSN: 0340-5354. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB Recently we described an enzyme-linked immunoadsorbent spot (ELISPOT) assay allowing us to define an immunological response profile observed in multiple sclerosis patients treated with Copaxone (**glatiramer acetate**; GA) but not untreated subjects [4]. The profile encompasses three criteria, a) reduced proliferative response to GA (as

observed with a standard primary proliferation assay); b) strong in vitro activation of interferon-gamma-producing T cells at high concentrations of GA (as detected by interferon-gamma ELISPOT); and c) activation of interleukin-4-producing T cells over a wider range of concentrations of GA (as detected by interleukin-4 ELISPOT). It is at present unknown whether the immunological response to GA correlates with the clinical response. To address this question we performed the pilot study reported here. We asked the major German multiple sclerosis centres to send us blood samples from all GA-treated patients who were going to discontinue treatment because of treatment failure. The clinical nonresponders either had an unchanged or increased exacerbation rate, or developed a secondary progressive course during GA treatment. Over more than one year, we prospectively collected 9 samples from clinical non-responders. We compared the immune response to GA of peripheral blood mononuclear cells from the 9 clinical nonresponders with 15 clinical responders, using a standard proliferation assay combined with ELISPOT assays for detection of interferon-gamma and interleukin-4 secreting cells. Thirteen (86 %) of the 15 clinical responders met at least 2 of the immunological response criteria mentioned above. In contrast, only 2 (22 %) of the 9 clinical nonresponders met two of the immunological criteria ($p = 0.0006$). We conclude that the ELISPOT assay may provide a promising additional tool for monitoring the treatment response in multiple sclerosis patients treated with GA.

L20 ANSWER 15 OF 23 MEDLINE on STN DUPLICATE 6

2002712535. PubMed ID: 12474988. Effect of combined IFNbeta-1a and **glatiramer acetate** therapy on GA-specific T-cell responses in multiple sclerosis. Dhib-Jalbut S; Chen M; Henschel K; Ford D; Costello K; Panitch H. (Department of Neurology, University of Maryland, Baltimore VA Medical Centre, Baltimore, Maryland 21201, USA.. sjalbut@umaryland.edu) . Multiple sclerosis (Houndmills, Basingstoke, England), (2002 Dec) 8 (6) 485-91. Journal code: 9509185. ISSN: 1352-4585. Pub. country: England: United Kingdom. Language: English.

AB The combined treatment with interferon beta (IFNbeta) and **glatiramer acetate** (GA) is of current interest in multiple sclerosis (MS). The therapeutic effect of GA in MS is believed to be mediated by GA-specific Th2 cells. IFNbeta has a significant anti-proliferative effect on GA-induced lymphoproliferation in vitro. Therefore, we examined the possibility that IFNbeta may interfere with the generation and phenotype of GA T-cell responses in MS patients receiving combined therapy. Sixty-six GA-specific T-cell lines (TCL) were generated ex vivo from five MS patients enrolled in an open-label dinical trial of combined IFNbeta/GA treatment. Controls included 83 pretreatment and 131 on-treatment GA-TCL from 11 MS patients treated with GA only, and five GA-TCL generated from four patients receiving IFNbeta-1a monotherapy. IFNgamma and IL-5 (**markers** of Th1 and Th2 responses, respectively) were assayed by ELISA in GA-TCL supematants. Th1/Th2 bias was defined by the IFNgamma/IL-5 level ratio (>2 = Th1 bias, <0.5 = Th2 bias, and 0.5-2 = Th0 bias). The frequency with which GA-reactive TCL were generated was 37.0% for the patients in the combination trial compared to 33.3% in the patients receiving GA alone. The mean stimulation index of the GA-TCL was 8.41 (range 2-42) for the combination compared to a mean of 6.29 (range 2-37) for the GA-treated group--a nonsignificant difference. Mean GA-TCL IFNgamma production was significantly lower in all treatment groups compared to pretreatment IL-5 levels were enhanced in all treatment groups compared to pretreatment levels, but the change was not statistically significant. The Th1/Th0/Th2 distribution of GA-TCL was 7%/30%/63% for the GA+IFNbeta group, 8%/9%/83% for the GA group, compared to 48%/21%/31% pre-GA treatment. All five GA-TCL from the IFNbeta-1a monotherapy patients were Th2-biased. We conclude that IFNbeta-1a does not affect the generation of GA-reactive T cells in vivo. Although more Th0 G4-TCL occurred with combination therapy than with G4 treatment alone, both groups shared an overall Th2 bias. Therefore, we speculate that combined therapy is unlikely to reduce the efficacy of GA treatment in MS.

L20 ANSWER 16 OF 23 MEDLINE on STN DUPLICATE 7
2002150787. PubMed ID: 11839841. MRI metrics as surrogate **markers** for clinical relapse rate in relapsing-remitting MS patients. Sormani Maria Pia; Bruzzi Paolo; Comi Giancarlo; Filippi Massimo. (Unit of Clinical Epidemiology and Trials, National Institute for Cancer Research, Genoa, Italy.) Neurology, (2002 Feb 12) 58 (3) 417-21. Journal code: 0401060. ISSN: 0028-3878. Pub. country: United States. Language: English.

AB OBJECTIVE: To formally validate metrics derived from conventional MRI as surrogate endpoints for relapse rate in MS. BACKGROUND: Although metrics derived from MRI are used widely in clinical trials of MS, a formal statistical validation of MRI metrics as surrogate endpoints for clinical outcome in MS is lacking. METHODS: A validation procedure was applied to clinical and MRI data collected in the context of a randomized, double-blind, placebo-controlled trial of **glatiramer acetate** in patients with relapsing-remitting MS. The four Prentice operational criteria were applied to assess surrogacy for the number of new enhancing lesions, the percentage change of T2 lesion volume, and a composite MRI score based on these two metrics. RESULTS: The results of this analysis show that all three MRI measures considered by the authors had a behavior compatible with the Prentice criteria for valid surrogates. The composite MRI score correlated with relapses and accounted for much of the treatment effect on relapse rate. CONCLUSIONS: This preliminary study suggests that conventional MRI metrics might serve as valid surrogate endpoints in MS trials with **glatiramer acetate** or treatments thought to have a similar mode of action.

L20 ANSWER 17 OF 23 MEDLINE on STN DUPLICATE 8
2002288131. PubMed ID: 12027786. Differentiation of multiple sclerosis subtypes: implications for treatment. Bitsch Andreas; Bruck Wolfgang. (Department of Neurology, Ruppiner Kliniken GmbH, Neuruppin, Germany.. wolfgang.brueck@charite.de) . CNS drugs, (2002) 16 (6) 405-18. Ref: 76. Journal code: 9431220. ISSN: 1172-7047. Pub. country: New Zealand. Language: English.

AB There has been tremendous progress in the immunomodulatory treatment of multiple sclerosis (MS) during recent years. With the introduction of interferon-beta, **glatiramer acetate** and mitoxantrone (recently registered for MS in the US), there are at least three therapeutic strategies that have proven effective in large phase III studies. However, not all patients with MS respond well to treatment with these drugs. This may largely be a consequence of disease heterogeneity. From a clinical perspective, patients with different disease courses show different treatment responses. Patients with relapsing-remitting MS are more likely to respond to immunomodulatory therapy than those with a progressive disease course. Studies of patients with secondary progressive MS have yielded inconsistent results and, so far, there has been no positive phase III study of immunomodulatory therapy in patients with primary progressive MS. Pathological evidence indicates that subtyping based on clinical findings alone does not reflect actual disease heterogeneity. In a large series of biopsy and autopsy specimens, at least four subtypes could be identified with respect to oligodendrocyte/myelin pathology and immunopathology. As long as the only method of identifying subtypes of disease is histopathology, differential therapy will remain a future goal. Thus, there is an urgent need for in vivo **markers** of immunopathogenesis in an individual patient that would allow treatment to be specifically directed towards a given pathological focus. However, at least from a theoretical point of view, some therapeutic approaches appear very attractive. Plasmapheresis and/or intravenous immunoglobulins could most plausibly be the best approach for the immunopathological subtype of MS, which is characterised by antibody and complement deposition next to demyelinated axons, in order to remove antibodies. The subtype of MS that is associated with heavy macrophage activation, T cell infiltration and expression of inflammatory mediator molecules, including tumour necrosis factor-alpha, may be most likely to respond to immunomodulation with interferon-beta or **glatiramer**

acetate. There are other subtypes of MS in which viral infection or oligodendrocyte degeneration, rather than autoimmunity, appear to play a role. It is possible that these could benefit from antiviral therapy, oligodendrocyte protection or oligodendrocyte transplantation, although therapies based on these latter approaches have yet to be developed.

L20 ANSWER 18 OF 23 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

2004:748708 The Genuine Article (R) Number: 845IJ. Issues and practices in multiple sclerosis. Burks J S (Reprint); Arnason B G; Coyle P K; Ford C C; Noronha A; Rammohan K W. Univ Nevada, Sch Med, Washoe Inst Neurosci, 4925 Pine Bluff Trail, Reno, NV 89509 USA (Reprint); Univ Nevada, Sch Med, Washoe Inst Neurosci, Reno, NV 89509 USA; Univ Chicago, Pritzker Sch Med, Chicago, IL 60637 USA; SUNY Stony Brook, Stony Brook MS Comprehens Care Ctr, Stony Brook, NY 11794 USA; SUNY Stony Brook, Hlth Sci Ctr, Stony Brook, NY 11794 USA; Univ New Mexico, Hlth Sci Ctr, Dept Neurol, Albuquerque, NM 87131 USA; Univ New Mexico, Hlth Sci Ctr, Clin & Magnet Resonance Res Ctr, Albuquerque, NM 87131 USA; Univ New Mexico, Hlth Sci Ctr, Multiple Sclerosis Specialty Clin, Albuquerque, NM 87131 USA; Univ Chicago, Dept Neurol, Chicago, IL 60637 USA; Ohio State Univ, MS Ctr, Columbus, OH 43210 USA. jackburks@aol.com. NEUROREHABILITATION AND NEURAL REPAIR (DEC 2002) Vol. 16, No. 4, pp. 307-320. ISSN: 1545-9683. Publisher: SAGE PUBLICATIONS INC, 2455 TELLER RD, THOUSAND OAKS, CA 91320 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The objective of this roundtable discussion of experts in the field of multiple sclerosis (MS) was to summarize the current understanding of MS and its therapeutic options. The experts discussed subjects ranging from the etiology of MS to the current standards for patient care. Specific topics included the subtypes of MS, with a focus on the benign subtype, brain atrophy, the role of magnetic resonance imaging or "neuroimaging studies," disease-modifying therapies, biological **markers** as indicators of drug efficacy, and combination therapies. In addition, the experts speculated as to what will be available in the near future for the improved diagnosis and management of MS. This review summarizes,the main points of this discussion and is intended to serve as a reference for neurologists involved in the care of patients with MS.

L20 ANSWER 19 OF 23 MEDLINE on STN

2002409281. PubMed ID: 12163197. Sustained immunological effects of **Glatiramer acetate** in patients with multiple sclerosis treated for over 6 years. Chen M; Conway K; Johnson K P; Martin R; Dhib-Jalbut S. (University of Maryland School of Medicine, Baltimore, MD 21201, USA.) Journal of the neurological sciences, (2002 Sep 15) 201 (1-2) 71-7. Journal code: 0375403. ISSN: 0022-510X. Pub. country: Netherlands. Language: English.

AB The availability of a group of multiple sclerosis (MS) patients at the University of Maryland, who had participated in the pivotal Copaxone trial in the early 1990s, provided an opportunity to examine the long-term immunologic effects of **Glatiramer acetate** (GA) treatment in MS. Forty-eight GA-reactive T-cell lines (TCL) were generated from 10 MS patients who have been receiving GA treatment for 6-9 years. Proliferative responses, cytokine production, and cross-reactivity with myelin basic protein (MBP) and the MBP immunodominant peptide 83-99 were compared to responses obtained from 10 MS patients who were tested pretreatment and after a shorter period of treatment ranging from 1 to 10 months. The results indicate that while long-term treatment with GA results in a 2.9-fold decrease in the estimated precursor frequency of GA-reactive T-cells, the sustained response to GA remains Th2-biased and in part cross-reactive with MBP and MBP (83-99) as measured by proliferation and cytokine release assays. The results indicate that despite a drop in the precursor frequency of GA-reactive T-cells with long-term treatment, the sustained response remains predominantly Th2-biased and cross-reactive with MBP, which is consistent with the anti-inflammatory effects of the drug and bystander suppression.

L20 ANSWER 20 OF 23 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

2001:413115 Document No.: PREV200100413115. Methotrexate pulse therapy on MSFC and cellular immunology **markers** in patients with relapsing progressive multiple sclerosis. Wang, Danhua [Reprint author]; Dressman, Laurie A. [Reprint author]; Rose, Barbara [Reprint author]; Moreng, George [Reprint author]; Rowe, Elizabeth S. [Reprint author]; Rowe, Vernon [Reprint author]. Kansas City, MO, USA. Neurology, (April 24, 2001) Vol. 56, No. 8 Supplement 3, pp. A365-A366. print.
Meeting Info.: 53rd Annual Meeting of the American Academy of Neurology. Philadelphia, PA, USA. May 05-11, 2001. American Academy of Neurology.
CODEN: NEURAI. ISSN: 0028-3878. Language: English.

L20 ANSWER 21 OF 23 MEDLINE on STN DUPLICATE 9

2001499398. PubMed ID: 11548979. **Glatiramer acetate** induces a Th2-biased response and crossreactivity with myelin basic protein in patients with MS. Chen M; Gran B; Costello K; Johnson K; Martin R; Dhib-Jalbut S. (University of Maryland School of Medicine, Baltimore 21201, USA.) Multiple sclerosis (Houndmills, Basingstoke, England), (2001 Aug) 7 (4) 209-19. Journal code: 9509185. ISSN: 1352-4585. Pub. country: England: United Kingdom. Language: English.

AB Glatiromer acetate (GA) is an approved treatment for multiple sclerosis (MS). The proposed mechanism of action is the induction of GA-specific T cells characterized by protective anti-inflammatory Th2 response. We tested this hypothesis in 11 MS patients treated with GA from 1-19 months. Interferon-gamma and IL-5 (**markers** of Th1 and Th2 responses respectively) were assayed by ELISA in GA-specific T-cell lines (TCL) supernatants. Th1/Th2 bias was defined based on the ratio of IFN-gamma/IL-5 secretion. Fifty-eight pre-treatment and 75 on-treatment GA-specific TCL were generated. On-treatment mean IL-5 levels in GA-TCL increased significantly, whereas those for IFN-gamma were markedly reduced. Consequently, the ratio of IFN-gamma IL-5 also shifted in favor of a Th2 response. The percentage of GA-TCL classified as Th1 was decreased, whereas those classified as Th2 increased on-treatment as compared to pre-treatment. Some GA-specific TCL, (approximately 25%) generated during treatment secreted predominantly IL-5 in response to MBP and the immunodominant MBP peptide 83-99, indicating that these crossreactive antigens can act as partial agonists for GA-reactive TCL. These results strongly suggest that the mechanism of action of GA in MS involves the induction of crossreactive GA-specific T cells with a predominant Th2 cytokine profile.

L20 ANSWER 22 OF 23 CAPLUS COPYRIGHT 2005 ACS on STN

2000:227679 Document No. 132:264109 Copolymer 1 related polypeptides for use as molecular weight **markers** and for therapeutic use. Gad, Alexander; Lis, Dora (Yeda Research and Development Co., Ltd., Israel; Teva Pharmaceuticals USA, Inc.). PCT Int. Appl. WO 2000018794 A1 20000406, 72 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US22402 19990924. PRIORITY: US 1998-101693 19980925.

AB The copolymer 1 related polypeptides are capable of binding to HMC class II antigen, HLA-DR1, HLA-DR2, HLA-DR4, or antigen presenting cell. The copolymer 1 related polypeptides are useful as mol. weight **markers** for accurate determination of the mol. weight of **glatiramer acetate** and other copolymers. The present invention provides a plurality of mol. weight **markers** for determining the mol. weight of **glatiramer acetate** and other copolymers which display linear relationships between molar ellipticity and mol. weight, and between retention time and the

log of the mol. weight The mol. weight **markers** also optimally demonstrate biol. activity similar to **glatiramer acetate** or corresponding copolymers and can be used for treating or preventing various immune diseases.

L20 ANSWER 23 OF 23 MEDLINE on STN DUPLICATE 10
1998214393. PubMed ID: 9553777. Current immunotherapy in multiple sclerosis. Bashir K; Whitaker J N. (Department of Neurology, University of Alabama at Birmingham 35233-7340, USA.) Immunology and cell biology, (1998 Feb) 76 (1) 55-64. Ref: 90. Journal code: 8706300. ISSN: 0818-9641. Pub. country: Australia. Language: English.
AB The underlying pathophysiology of multiple sclerosis is presumed to be autoimmune in nature. Attempts to find an effective treatment for this common disease of the central nervous system have primarily focused on immune-mediated therapies, both immunosuppressive and immunomodulatory. The wide variety of immunological abnormalities detected in multiple sclerosis and its animal model, experimental allergic encephalomyelitis, has prompted the testing of a diverse array of drugs to be used for treatment. Recent successes in the treatment of relapsing-remitting multiple sclerosis with interferon beta and **glatiramer acetate** have renewed interest in and raised expectations for the effective control of this neurological disorder. Improved methodology in clinical trials, the development of surrogate **markers** and the availability of novel therapies bode well for more rapid advances.

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(FILE 'HOME' ENTERED AT 14:56:51 ON 26 JUL 2005)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 14:57:01 ON 26 JUL 2005

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L1          760 S MOLECULAR WEIGHT MARKER
L2            1 S L1 AND "GLAT"
L3            9 S L1 AND TYROSINE
L4            0 S L3 AND ALAINE
L5            0 S L3 AND ALANINE
L6            0 S L3 AND GLUTAMIC ACIE
L7            0 S L3 AND LYSINE
L8            2 DUP REMOVE L3 (7 DUPLICATES REMOVED)
L9            0 S L1 AND COPLYMER-1
L10           0 S L1 AND CALIBRATE
L11          36 S L1 AND CALIBRATION
L12           0 S L11 AND GLAT COPOLYMER
L13          13 DUP REMOVE L11 (23 DUPLICATES REMOVED)
L14          72 S "GLAT"
L15          17 S L14 AND COPAXONE
L16           7 DUP REMOVE L15 (10 DUPLICATES REMOVED)
L17        1464 S GLATIRAMER ACETATE
L18           0 S L17 AND CALIBRATION
L19          56 S L17 AND MARKERS
L20          23 DUP REMOVE L19 (33 DUPLICATES REMOVED)
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=> s l17 and molecular weight markers
L21           3 L17 AND MOLECULAR WEIGHT MARKERS

=> dup remove l21
PROCESSING COMPLETED FOR L21
L22           3 DUP REMOVE L21 (0 DUPLICATES REMOVED)

=> d l22 1-3 cbib abs
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L22 ANSWER 1 OF 3 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2004:431241 Document No.: PREV200400435798. Copolymer 1 related polypeptides for use as **molecular weight markers** and for

therapeutic use. Gad, Alexander [Inventor, Reprint Author]; Lis, Dora [Inventor]. Nes Ziona, Israel. ASSIGNEE: Yeda Research and Development Co., Ltd., Rehovot, Israel. Patent Info.: US 6800287 20041005. Official Gazette of the United States Patent and Trademark Office Patents, (Oct 5 2004) Vol. 1287, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133 (ISSN print). Language: English.

AB The present invention provides **molecular weight markers** for accurate determination of the molecular weight of **glatiramer acetate** and other copolymers. The present invention further provides a plurality of **molecular weight markers** for determining the molecular weight of **glatiramer acetate** and other copolymers which display linear relationships between molar ellipticity and molecular weight, and between retention time and the log of the molecular weight. The **molecular weight markers** also optimally demonstrate biological activity similar to **glatiramer acetate** or corresponding copolymers and can be used for treating or preventing various immune diseases.

L22 ANSWER 2 OF 3 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2003:129777 Document No.: PREV200300129777. Copolymer 1 related polypeptides for use as **molecular weight markers** and for therapeutic use. Gad, Alexander [Inventor, Reprint Author]; Lis, Dora [Inventor]. Nes Ziona, Israel. ASSIGNEE: Yeda Research and Development Co. Ltd. at the Weizmann Institute of Science, Israel. Patent Info.: US 6514938 20030204. Official Gazette of the United States Patent and Trademark Office Patents, (Feb 4 2003) Vol. 1267, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133 (ISSN print). Language: English.

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L22 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
2000:227679 Document No. 132:264109 Copolymer 1 related polypeptides for use as **molecular weight markers** and for therapeutic use. Gad, Alexander; Lis, Dora (Yeda Research and Development Co., Ltd., Israel; Teva Pharmaceuticals USA, Inc.). PCT Int. Appl. WO 2000018794 A1 20000406, 72 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US22402 19990924. PRIORITY: US 1998-101693 19980925.

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=> s (gad a?/au or lis d?/au)
L23 1096 (GAD A?/AU OR LIS D?/AU)

=> s l23 and glatiramer acetate
L24 9 L23 AND GLATIRAMER ACETATE

=> dup remove l24
PROCESSING COMPLETED FOR L24
L25 5 DUP REMOVE L24 (4 DUPLICATES REMOVED)

=> d l25 1-5 cbib abs

L25 ANSWER 1 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2004:431241 Document No.: PREV200400435798. Copolymer 1 related polypeptides for use as molecular weight markers and for therapeutic use. **Gad, Alexander** [Inventor, Reprint Author]; **Lis, Dora** [Inventor]. Nes Ziona, Israel. ASSIGNEE: Yeda Research and Development Co., Ltd., Rehovot, Israel. Patent Info.: US 6800287 20041005. Official Gazette of the United States Patent and Trademark Office Patents, (Oct 5 2004) Vol. 1287, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print). Language: English.
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L25 ANSWER 2 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2003:129777 Document No.: PREV200300129777. Copolymer 1 related polypeptides for use as molecular weight markers and for therapeutic use. **Gad, Alexander** [Inventor, Reprint Author]; **Lis, Dora** [Inventor]. Nes Ziona, Israel. ASSIGNEE: Yeda Research and Development Co. Ltd. at the Weizmann Institute of Science, Israel. Patent Info.: US 6514938 20030204. Official Gazette of the United States Patent and Trademark Office Patents, (Feb 4 2003) Vol. 1267, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print). Language: English.
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pharmaceutical compositions for the treatment of immune diseases comprising a polypeptide having an identified molecular weight and an amino acid composition corresponding to **glatiramer acetate** or a terpolymer.

L25 ANSWER 3 OF 5 MEDLINE on STN DUPLICATE 1
2002386520. PubMed ID: 12134954. Regional peptide uptake study in the rat intestinal mucosa: **glatiramer acetate** as a model drug.
Haupt Susan; Gil Efrat; Tirosh Regin; Klinger Ety; **Gad Alexander**; Rubinstein Abraham. (The Hebrew University of Jerusalem, Faculty of Medicine, School of Pharmacy, Israel.) Pharmaceutical research, (2002 Jun) 19 (6) 832-7. Journal code: 8406521. ISSN: 0724-8741. Pub. country: United States. Language: English.

AB PURPOSE: To identify regions of the rat intestine that are able to internalize from the lumen oligopeptides, using the model drug **glatiramer acetate** (GA). METHODS: GA was introduced into rat intestinal sacs and the integrity of GA during uptake was monitored using antibody detection. Sodium docecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting of intestinal homogenates that had been exposed to GA were performed to identify GA presence. An enzyme-linked immunosorbent assay (ELISA) protocol was adapted for GA quantification. Immunohistochemistry was undertaken to examine the rat colonic wall for GA uptake, and confocal microscopy was used to differentiate adsorbed and internalized peptide in cultured colorectal adenocarcinoma cells. RESULTS: The colon and the ileum, respectively, were identified to be the intestinal regions in which GA was maximally preserved during uptake from the lumen. GA was identified to cross the colonic wall from the epithelium to the serosa. Internalization of GA into cultured colonic epithelial cells was demonstrated. CONCLUSIONS: The rat colonic wall was identified to be less proteolytically active toward GA compared to the wall of the more proximal regions of the small intestine. GA has the capacity to penetrate from the lumen into the colonic wall. The maintenance of GA integrity within the wall of the colon offers the potential for local biological activity of the drug.

L25 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
2002:350405 Document No. 138:100305 **Glatiramer acetate** analysis in the mucosa of the rat intestine. Haupt, S.; Gil, E.; Tirosh, R.; Klinger, E.; **Gad, A.**; Rubinstein, A. (School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, 91120, Israel). Proceedings - 28th International Symposium on Controlled Release of Bioactive Materials and 4th Consumer & Diversified Products Conference, San Diego, CA, United States, June 23-27, 2001, Volume 2, 866-867. Controlled Release Society: Minneapolis, Minn. (English) 2001. CODEN: 69CNY8.

AB **Glatiramer acetate** (GA) introduced into sacs of the rat intestine was detected in intestinal wall fractions. In intestinal segments without luminal contents GA degraded faster in proximal regions compared with the colon. Fecal meter caused rapid degradation of GA in the colon.

L25 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
2000:227679 Document No. 132:264109 Copolymer 1 related polypeptides for use as molecular weight markers and for therapeutic use. **Gad, Alexander; Lis, Dora** (Yeda Research and Development Co., Ltd., Israel; Teva Pharmaceuticals USA, Inc.). PCT Int. Appl. WO 2000018794 A1 20000406, 72 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO

1999-US22402 19990924. PRIORITY: US 1998-101693 19980925.
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=> s l23 and molecular weight markers
L26 3 L23 AND MOLECULAR WEIGHT MARKERS

=> dup remove l26
PROCESSING COMPLETED FOR L26
L27 3 DUP REMOVE L26 (0 DUPLICATES REMOVED)

=> d l27 1-3 cbib abs

L27 ANSWER 1 OF 3 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2004:431241 Document No.: PREV200400435798. Copolymer 1 related polypeptides for use as **molecular weight markers** and for therapeutic use. **Gad, Alexander** [Inventor, Reprint Author]; **Lis, Dora** [Inventor]. Nes Ziona, Israel. ASSIGNEE: Yeda Research and Development Co., Ltd., Rehovot, Israel. Patent Info.: US 6800287 20041005. Official Gazette of the United States Patent and Trademark Office Patents, (Oct 5 2004) Vol. 1287, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print). Language: English.
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L27 ANSWER 2 OF 3 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2003:129777 Document No.: PREV200300129777. Copolymer 1 related polypeptides for use as **molecular weight markers** and for therapeutic use. **Gad, Alexander** [Inventor, Reprint Author]; **Lis, Dora** [Inventor]. Nes Ziona, Israel. ASSIGNEE: Yeda Research and Development Co. Ltd. at the Weizmann Institute of Science, Israel. Patent Info.: US 6514938 20030204. Official Gazette of the United States Patent and Trademark Office Patents, (Feb 4 2003) Vol. 1267, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print). Language: English.
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L27 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
2000:227679 Document No. 132:264109 Copolymer 1 related polypeptides for use as **molecular weight markers** and for therapeutic use. **Gad, Alexander; Lis, Dora** (Yeda Research and Development Co., Ltd., Israel; Teva Pharmaceuticals USA, Inc.). PCT Int. Appl. WO 2000018794 A1 20000406, 72 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US22402 19990924. PRIORITY: US 1998-101693 19980925.
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=> s l23 and GLAT
L28 1 L23 AND GLAT

=> d l28 cbib abs

L28 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
2000:227679 Document No. 132:264109 Copolymer 1 related polypeptides for use as molecular weight markers and for therapeutic use. **Gad, Alexander; Lis, Dora** (Yeda Research and Development Co., Ltd., Israel; Teva Pharmaceuticals USA, Inc.). PCT Int. Appl. WO 2000018794 A1 20000406, 72 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US22402 19990924. PRIORITY: US 1998-101693 19980925.
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=> s l23 and copolymer-1
L29 5 L23 AND COPOLYMER-1

=> dup remove l29
PROCESSING COMPLETED FOR L29
L30 4 DUP REMOVE L29 (1 DUPLICATE REMOVED)

=> d l30 1-4 cbib abs

L30 ANSWER 1 OF 4 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2004:431241 Document No.: PREV200400435798. **Copolymer 1** related polypeptides for use as molecular weight markers and for therapeutic use. **Gad, Alexander** [Inventor, Reprint Author]; **Lis, Dora** [Inventor]. Nes Ziona, Israel. ASSIGNEE: Yeda Research and Development Co., Ltd., Rehovot, Israel. Patent Info.: US 6800287 20041005. Official Gazette of the United States Patent and Trademark Office Patents, (Oct 5 2004) Vol. 1287, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print). Language: English.
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L30 ANSWER 2 OF 4 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2003:129777 Document No.: PREV200300129777. **Copolymer 1** related polypeptides for use as molecular weight markers and for therapeutic use. **Gad, Alexander** [Inventor, Reprint Author]; **Lis, Dora** [Inventor]. Nes Ziona, Israel. ASSIGNEE: Yeda Research and Development Co. Ltd. at the Weizmann Institute of Science, Israel. Patent Info.: US 6514938 20030204. Official Gazette of the United States Patent and Trademark Office Patents, (Feb 4 2003) Vol. 1267, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print). Language: English.
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L30 ANSWER 3 OF 4 MEDLINE on STN DUPLICATE 1
2002386520. PubMed ID: 12134954. Regional peptide uptake study in the rat intestinal mucosa: glatiramer acetate as a model drug. Haupt Susan; Gil Efrat; Tirosh Regin; Klinger Ety; **Gad Alexander**; Rubinstein Abraham. (The Hebrew University of Jerusalem, Faculty of Medicine, School

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AB PURPOSE: To identify regions of the rat intestine that are able to internalize from the lumen oligopeptides, using the model drug glatiramer acetate (GA). METHODS: GA was introduced into rat intestinal sacs and the integrity of GA during uptake was monitored using antibody detection. Sodium docecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting of intestinal homogenates that had been exposed to GA were performed to identify GA presence. An enzyme-linked immunosorbent assay (ELISA) protocol was adapted for GA quantification. Immunohistochemistry was undertaken to examine the rat colonic wall for GA uptake, and confocal microscopy was used to differentiate adsorbed and internalized peptide in cultured colorectal adenocarcinoma cells. RESULTS: The colon and the ileum, respectively, were identified to be the intestinal regions in which GA was maximally preserved during uptake from the lumen. GA was identified to cross the colonic wall from the epithelium to the serosa. Internalization of GA into cultured colonic epithelial cells was demonstrated. CONCLUSIONS: The rat colonic wall was identified to be less proteolytically active toward GA compared to the wall of the more proximal regions of the small intestine. GA has the capacity to penetrate from the lumen into the colonic wall. The maintenance of GA integrity within the wall of the colon offers the potential for local biological activity of the drug.

L30 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN

2000:227679 Document No. 132:264109 **Copolymer 1** related polypeptides for use as molecular weight markers and for therapeutic use. **Gad, Alexander; Lis, Dora** (Yeda Research and Development Co., Ltd., Israel; Teva Pharmaceuticals USA, Inc.). PCT Int. Appl. WO 2000018794 A1 20000406, 72 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US22402 19990924. PRIORITY: US 1998-101693 19980925.

AB The **copolymer 1** related polypeptides are capable of binding to HMC class II antigen, HLA-DR1, HLA-DR2, HLA-DR4, or antigen presenting cell. The **copolymer 1** related polypeptides are useful as mol. weight markers for accurate determination of the mol. weight of glatiramer acetate and other copolymers. The present invention provides a plurality of mol. weight markers for determining the mol. weight of glatiramer acetate and other copolymers which display linear relationships between molar ellipticity and mol. weight, and between retention time and the log of the mol. weight The mol. weight markers also optimally demonstrate biol. activity similar to glatiramer acetate or corresponding copolymers and can be used for treating or preventing various immune diseases.

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